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Zafgen Announces Positive Topline Phase 1b Data for ZGN-433 in Obesity

Findings Show MetAP2 Inhibition Treatment Drives Significant Weight Loss with Excellent Tolerability and Favorable Metabolic Effects

CAMBRIDGE, Mass., January 5, 2011 – Zafgen, Inc., a pharmaceutical company pioneering novel obesity therapeutics to help the body regain and sustain a lean, healthy state by targeting imbalances in fat metabolism, today announced positive topline results from its Phase 1b study of ZGN-433, a methionine aminopeptidase 2 inhibitor (MetAP2), for the treatment of severe obesity. The Phase 1b study met its primary and secondary objectives and showed that ZGN-433 at a dose of 0.9 mg/m2 was well tolerated and reduced body weight by a median value of 1 kg per week and 3.1 percent over 26 days relative to placebo in severely obese subjects. MetAP2 inhibitors work by re-establishing balance to the ways the body metabolizes fat, leading to substantial loss of body weight.

The results of the study also demonstrated a decline in hunger as well as meaningful changes in lipid parameters following treatment at 0.9 mg/m2. These changes included a 38 percent reduction in triglyceride levels and a 23 percent reduction in low-density lipoprotein (LDL) cholesterol levels ($p<0.05$). Additionally, beta-hydroxybutyrate, an indicator of fat oxidation, increased to levels seen with very low-energy diets. No treatment-related serious adverse events were observed. The data will be presented at the Keystone Symposia on Obesity in Keystone, Colo., on January 15, at 2:30 p.m. MST during the “Hot Topics in Obesity Therapy” workshop.

“These findings are significant as they show MetAP2 inhibition has the potential to drive impressive weight loss with excellent tolerability and favorable metabolic effects in severely obese individuals, and demonstrate that the preclinical pharmacology of ZGN-433 is translating well to human studies,” said Thomas Hughes, Ph.D., president and chief executive officer, Zafgen, Inc. “The results show the magnitude of weight loss approaches the commonly recommended maximal rate of safe weight loss, which is exceeded only by gastric bypass surgery, duodeno-jejunal bypass liner and restrictive therapy. If sustained, the rate of weight loss would be consistent with a 6-9 month course of treatment in individuals requiring a 20-40 percent reduction in weight.”

A double-blind, placebo-controlled multiple ascending dose study was performed to evaluate the safety and preliminary efficacy of ZGN-433 in reducing weight in severely obese females with a body mass index (BMI) between 32-45 with co-morbidities allowed. Twenty-four people were enrolled in the core study. The primary objective of the study was to evaluate the safety and tolerability, and determine the pharmacokinetics and pharmacodynamics of ZGN-433 in obese individuals. The secondary objective was to obtain information on weight loss in obese individuals exposed to eight intravenous doses of ZGN-433 administered over a four-week period. Patients were allowed to eat normally and were not counselled to exercise. Individuals received ZGN-433 or placebo twice weekly by intravenous administration over a four-week treatment period for a total of eight doses at three different dose levels (0.22, 0.65, and 1.96 mg per administration).

“ZGN-433 has the potential to be the first drug to produce weight loss approaching that of bariatric surgery,” said Steven R. Smith, M.D., scientific director of the Translational Research Institute for Metabolism and Diabetes and professor at the Sanford-Burnham Medical Research Institute in Orlando. “Given the excellent tolerability and safety seen in this four-week study, the program shows early promise to provide a positive risk/benefit proposition. While the long-term safety and efficacy of the compound remain to be established, there is nothing in the industry drug pipeline this advanced that has shown this kind of efficacy. These early results are very encouraging, and there remains a significant unmet medical need for new obesity therapeutics that are both safe and efficacious.”

“While Zafgen’s understanding of the compound’s mechanism of action has evolved significantly since the company’s early days, MetAP2 inhibition for the treatment of obesity and diabetes appears to translate well across species,” said Alan D. Cherrington, Ph.D., professor of medicine and molecular physiology and biophysics, Vanderbilt University, and former American Diabetes Association president. “These positive initial clinical and preclinical findings show that MetAP2 inhibitor actions point to utility for the treatment of severe obesity, and also show intriguing potential for use in broader indications related to control of glucose, lipid and cholesterol metabolism, including hepatic glucose intolerance, fatty liver and dyslipidemia.”

Zafgen is pioneering novel obesity therapeutics to help the body regain and sustain a lean, healthy state by targeting imbalances in fat metabolism. Research has shown that fat metabolism differs between obese and lean individuals. Recent studies indicate that once a person becomes obese, the body undergoes certain changes and is “programmed” to make and store more fat. These metabolic adaptations that take place in obese people impair the normal release of fatty acids from adipose tissue and restrict the ability to stimulate formation of ketone bodies (a byproduct of the breakdown of fatty acids). Simultaneously, the body becomes much more efficient in diverting calories from food and storing them as fat.

About ZGN-433
Zafgen's lead compound, ZGN-433, is being studied as a pharmacological alternative to bariatric surgery for severe obesity. The company plans to initiate Phase 2a studies with ZGN-433 administered via subcutaneous injection in 2011. Zafgen is also developing new compounds suitable for oral administration for use in broader indications as part of its second generation program. ZGN-433 was initially developed by CKD Pharmaceuticals. The molecule was originally profiled for efficacy in the treatment of solid tumors. Zafgen holds exclusive worldwide rights (exclusive of Korea) for development and commercialization of ZGN-433.

About Obesity and Fat Metabolism
Obesity continues to be one of the world's most costly and underserved health issues. As such, there exists a tremendous unmet medical need for effective drug therapies to treat obesity, which has reached epidemic proportions and is growing at an alarming rate. According to the Worldwide Health Organization (WHO), the number of obese adults had increased to at least 400 million worldwide in 2005, with more than 700 million projected by 2015[1]. If current trends continue, 103 million American adults will be considered obese by 2018[2]. The U.S. is expected to spend $344 billion on health care costs attributable to obesity in 2018 if rates continue to increase at their current levels with obesity‐related direct expenditures expected to account for more than 21 percent of the nation's direct health care spending in 2018[2].

Obesity leads to serious health consequences. As BMI increases, so does one's risk for chronic diseases such as cardiovascular disease, diabetes, musculoskeletal disorders and some cancers, compounding the urgency for new and effective treatment options1. Currently available weight loss treatments function by blocking fat absorption or signalling feelings of fullness or diminished appetite in the brain. These drugs are often associated with undesirable side effects and limited efficacy that fails to provide sustainable weight loss in many patients.

About Zafgen, Inc.
Zafgen is pioneering novel obesity therapeutics that directly target fat metabolism to help the body regain and sustain a lean, healthy state. The company's approach focuses on restoring control of key metabolic processes, releasing stored fat which then is used by the body as fuel. Zafgen's first generation product, named ZGN-433, is being studied in a Phase 1b clinical trial for its use as a pharmacological alternative to bariatric surgery in the treatment of severe obesity. Zafgen's leadership and scientific advisors include leading experts in obesity, metabolic disorders and medicinal chemistry. Founded in 2005, the company is located in Cambridge, Mass. For more information, visit www.zafgen.com.